



Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

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Key Considerations and Recommendations

- Selection of tuberculosis (TB)-preventive treatment for individuals with HIV and latent tuberculosis infection (LTBI) should be based on the individual's antiretroviral therapy (ART) regimen as noted below:
 - Any ART regimen can be used when isoniazid alone is used for LTBI treatment (AIII).
 - Efavirenz 600 mg once daily or raltegravir 400 mg twice daily-based regimens (in combination with either abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine) can be used without dose adjustment with once-weekly isoniazid plus rifapentine (AII).
 - If rifampin or rifapentine is used to treat LTBI, clinicians should review Tables 21a through 21e to assess the potential for drug-drug interactions among different antiretroviral (ARV) drugs and the rifamycins (AIII).
- All patients with HIV and active TB who are not on ART should be started on ART as described below:
 - **CD4 T lymphocyte (CD4) cell counts <50 cells/mm³**: Initiate ART as soon as possible, but within 2 weeks of starting TB treatment (AI).
 - **CD4 counts ≥50 cells/mm³**: Initiate ART within 8 weeks of starting TB treatment (AI).
 - **During pregnancy, regardless of CD4 count**: Initiate ART as early as feasible, for treatment of the person with HIV and to prevent HIV transmission to the infant (AIII).
 - **With tuberculous meningitis**: When initiating ART early, patients should be closely monitored as high rates of adverse events and deaths have been reported in a randomized trial (AI).
- For patients with active TB who are receiving ART, the ARV regimen should be assessed with particular attention to potential drug-drug interactions between ARVs and TB drugs. The ARV regimen may need to be modified to permit use of the optimal TB treatment regimen (see Tables 21a through 21e for dosing recommendations).
- Rifamycin antibiotics (rifabutin, rifampin, and rifapentine), are critical components of TB treatment regimens and should be included in regimens for patients with both HIV and active TB, unless precluded because of TB resistance or toxicity. However, rifamycin antibiotics have a considerable potential for drug-drug interactions. Clinicians should review Tables 21a through 21e to assess the potential for interactions among different ARV drugs and the rifamycins (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Managing Latent Tuberculosis Infection in Persons with HIV

Approximately 23% of the world's population has tuberculosis (TB), with a 5% to 10% lifetime risk of progressing to active disease.¹ Among individuals with TB infection, the risk of developing active TB is much higher among those who also have HIV, and this risk increases as immune deficiency worsens.²

Tuberculosis Preventive Treatment

Randomized controlled clinical trials have demonstrated that treatment for latent tuberculosis infection (LTBI) in people with HIV reduces risk of active TB, especially in those with a positive tuberculin skin test.³ After active TB disease has been excluded, the Centers for Disease Control and Prevention (CDC) recommends one of the following regimens for LTBI treatment (see [Treatment Regimens for Latent TB Infection \(LTBI\), Adult and Adolescent Opportunistic Infection Guidelines](#)):

- Isoniazid daily or twice weekly for 6 or 9 months
- Isoniazid plus rifapentine once weekly for 12 weeks
- Rifampin daily for 4 months.

For more than 30 years, isoniazid has been the cornerstone of treatment for LTBI to prevent active TB. It can be coadministered with any antiretroviral (ARV) regimen. The combination of isoniazid and rifapentine administered once a week for 12 weeks as directly observed therapy (DOT) was as safe and effective as 9 months of isoniazid alone in preventing TB in patients with HIV who were not on ART in the PREVENT Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

TB study.⁴ Another study randomized 1,148 South African adults with HIV to one of four treatment groups: rifapentine plus isoniazid weekly for 12 weeks, rifampin plus isoniazid twice weekly for 12 weeks, isoniazid daily for 6 months, or continuous isoniazid therapy. TB incidence did not differ among the groups.⁵ Similarly, in 3,000 people with HIV infection in the BRIEF TB study, there was no difference in TB incidence between those who received rifapentine plus isoniazid daily for 1 month and those who received 9 months of daily isoniazid.⁶ There were fewer adverse events and a higher treatment completion rate with the 1-month regimen than with 9 months of isoniazid alone. However, this short-course regimen has not yet been endorsed by the World Health Organization or CDC.

Although rifapentine induces cytochrome P (CYP) 450 isoenzymes and can potentially cause significant drug-drug interactions, there are pharmacokinetic (PK) data supporting its use, daily or once weekly with efavirenz (EFV) 600 mg daily,^{7,8} and once weekly with raltegravir (RAL) 400 mg twice daily (AII).⁹ A healthy volunteer study of dolutegravir (DTG) and weekly rifapentine with isoniazid was stopped early following the development of an influenza-like syndrome and elevated aminotransferase levels in two of the first four participants after the third rifapentine-isoniazid dose.¹⁰ However, in a Phase 1/2 study of 60 adults with HIV on DTG-based ART and weekly rifapentine with isoniazid, coadministration of the regimens was well tolerated.¹¹ Although the rifapentine-isoniazid regimen decreased DTG trough concentrations by 50% to 60%, all but one remained above the DTG IC₉₀ and all HIV viral loads remained suppressed. Until more clinical data are available on the safety and efficacy of DTG use with rifapentine, the Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) does not recommend DTG use with once weekly rifapentine-isoniazid (AIII). Rifampin for 4 months may also be considered for TB preventive treatment, but clinicians should pay careful attention to potential drug-drug interactions with specific ARV drugs (see Tables 21a through 21e).

A randomized trial of isoniazid preventive therapy (IPT) that compared isoniazid initiated during pregnancy (immediate IPT) to delayed until 12 weeks postpartum (deferred IPT) in 956 women with HIV on ART. This study demonstrated a greater number of adverse pregnancy outcomes in women on immediate IPT. Treatment-related maternal adverse events were higher than expected in both arms, suggesting that IPT should be delayed until after delivery.¹² IPT is still recommended, however, for pregnant women with HIV whose close household contacts include a person with TB disease ([Adult and Adolescent Opportunistic Infection Guidelines](#)).

If a patient with HIV is a contact of an individual with drug-resistant TB, the options for LTBI treatment should be modified. In this setting, consultation with a TB expert is advised.

Impact of Antiretroviral Therapy in Preventing Active Tuberculosis

Accumulating evidence suggests that ART can prevent active TB. The TEMPRANO study conducted in Côte d'Ivoire randomized 2,056 participants with HIV to one of four study arms: deferred ART, deferred ART plus IPT, early ART, or early ART plus IPT. The initial results demonstrated that IPT and early ART each independently reduced the risk of a serious HIV-related event, many of which were tuberculosis, and that IPT with early ART provided the best protection from disease.¹³ Data from longer follow-up (median 4.9 years) showed that 6 months of IPT given early in the course of HIV infection provided a durable survival benefit, with a 37% reduction in the risk of death that was independent of ART.¹⁴ In the START study, 4,685 participants with CD4 T lymphocyte (CD4) cell counts >500 cells/mm³ were randomized to receive immediate ART or ART deferred until their CD4 count dropped to 350 cells/mm³ or until they developed a clinical condition that required ART. TB was one of the three most common clinical events, occurring in 14% of participants in the immediate ART group and 20% of participants in the deferred ART group.¹⁵ Collectively, these two large randomized studies showed that early initiation of ART (with or without IPT) reduced active TB, particularly in countries with high prevalence of TB/ HIV coinfection.

Antiretroviral Therapy for Patients with HIV and Active Tuberculosis

Active pulmonary or extrapulmonary TB disease requires prompt initiation of TB treatment. The treatment of active TB disease in patients with HIV should follow the general principles guiding treatment for patients without HIV. The [Adult and Adolescent Opportunistic Infection Guidelines](#) include a more complete discussion of the diagnosis and treatment of TB disease in patients with HIV.

All patients with HIV/TB disease should be treated with ART (**AI**) though the timing of initiation of ART may vary as discussed below. Important considerations related to the use of ART in patients with active TB disease include:

- When to start ART;
- Significant PK drug-drug interactions between anti-TB and ARV agents;
- The additive toxicities associated with concomitant ARV and anti-TB drug use; *and*
- The development of TB-associated immune reconstitution inflammatory syndrome (IRIS) after ART initiation.

Tuberculosis Diagnosed While a Patient is Receiving Antiretroviral Therapy

ART should be continued when TB is diagnosed in a patient receiving ART, but the ARV regimen should be assessed with particular attention to potential drug interactions between ARVs and TB drugs (discussed below). The patient's ARV regimen may need to be modified to permit use of the optimal TB treatment regimen (see Tables [18a](#) through [18e](#) for dosing recommendations).

Tuberculosis Diagnosed in a Patient Not Yet Receiving Antiretroviral Therapy

ART should not be delayed until TB treatment is completed, as this strategy was associated with higher mortality rates in the SAPI-T-1 study.¹⁶ The timing of ART in specific patient populations is discussed below.

Patients with CD4 Counts <50 cells/mm³: Three large randomized clinical trials in patients with HIV/TB disease, conducted in Africa and Asia, all convincingly showed that early ART in those with CD4 counts <50 cell/mm³ significantly reduced AIDS events or deaths.¹⁷⁻¹⁹ In these studies, early ART was defined as starting ART within 2 weeks of and no later than 4 weeks after initiation of TB therapy. In all three studies, IRIS was more common in patients initiating ART earlier than in patients starting ART later, but the syndrome was infrequently associated with mortality. Collectively these three trials support initiation of ART within the first 2 weeks of TB treatment in patients with CD4 counts <50 cells/mm³ (**AI**).

Patients with CD4 Counts ≥50 cells/mm³: In the three studies mentioned above,¹⁷⁻¹⁹ there was no survival benefit for patients with CD4 counts ≥50 cells/mm³ who initiated ART at <2 weeks versus later (8 to 12 weeks) after beginning TB treatment. Importantly, none of the studies demonstrated harm from earlier ART initiation, and there are many well-documented benefits from ART in people with HIV regardless of TB coinfection. It is unlikely that more trials will be conducted to specifically inform the decision on when to start ART in patients with TB and CD4 counts >50 cells/mm³. However, given the growing body of evidence supporting early ART in general and lack of data showing any harm in patients with TB coinfection, the Panel recommends ART initiation within 8 weeks of starting TB treatment for patients with CD4 counts ≥50 cells/mm³ (**AI**).

Patients with Drug-Resistant TB: Mortality rates in patients with multidrug-resistant or extensively drug-resistant TB and HIV are very high.²⁰ Retrospective case control studies and case series provide growing evidence of better outcomes associated with receipt of ART in such patients,^{21,22} but the optimal timing for initiation of ART is unknown. Management of patients with HIV and drug-resistant TB is complex, and expert consultation is encouraged (**BIII**).

Patients with TB Meningitis: TB meningitis is often associated with severe complications and a high

mortality rate. In a study conducted in Vietnam, patients with HIV-associated TB meningitis were randomized to immediate ART or to ART deferred until 2 months after initiation of TB treatment. A significantly higher rate of severe (Grade 4) adverse events was seen in patients who received immediate ART than in those who received deferred ART (80.3% vs. 69.1% for immediate and deferred ART, respectively; $P = 0.04$).²³ Despite these study results, many experts would recommend initiating ART within 2 to 8 weeks of starting anti-TB treatment, opting for 2 weeks in individuals with CD4 counts <50 cells/mm³ in settings in which close monitoring of drug-related toxicities and central nervous system adverse events is feasible (see [Adult and Adolescent Opportunistic Infection Guidelines](#)) (BIII). Managing patients with HIV and TB meningitis is complex, and expert consultation is encouraged (BIII).

Pregnant Patients: All pregnant individuals with HIV and active TB should be started on ART as early as feasible, both for treatment of the person with HIV and to prevent HIV transmission to the infant (AIII). The choice of ART should be based on efficacy and safety in pregnancy and should take into account potential drug-drug interactions between ARVs and rifamycins (see [Perinatal Guidelines](#) for more detailed discussions).

Drug Interaction Considerations

Rifamycin antibiotics (rifabutin, rifampin, and rifapentine), are a crucial component of TB treatment regimens. However, they are associated with a considerable potential for drug interactions. Rifampin is a potent inducer of the hepatic CYP450 (mostly 3A and 2C subfamilies), P-glycoprotein (P-gp), and uridine diphosphate glucuronosyltransferase 1A1 enzymes. Rifabutin and rifapentine are CYP3A4 substrates and inducers. As potent enzyme inducers, the rifamycin antibiotics can accelerate drug metabolism, resulting in significant reduction in ARV drug exposure. The ARV drugs most affected include all protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), the integrase strand transfer inhibitors (INSTIs), and the CCR5 antagonist maraviroc (MVC). Most nucleos(t)ide reverse transcriptase inhibitors (NRTIs), the fusion inhibitor enfuvirtide, and the CD4 post attachment inhibitor ibalizumab are not expected to have significant drug interactions with the rifamycins. Tables 21a through 21e outline the magnitude of these interactions and provide dosing recommendations when rifamycin antibiotics and selected ARV drugs are used concomitantly.

Because tenofovir alafenamide (TAF) is a P-gp substrate, its plasma concentrations may be reduced by rifamycin antibiotics. Current labeling does not recommend concomitant administration of TAF and any rifamycin antibiotic.²⁴ However, in a healthy volunteer study, following administration of TAF/emtricitabine with rifampin, intracellular tenofovir-DP concentrations were still 4.2-fold higher than those achieved by tenofovir disoproxil fumarate.²⁵ A clinical trial in persons with HIV and TB with concomitant use of TAF and rifampin is ongoing.

Several ARV drugs are not recommended for use with rifampin; clinicians should refer to Tables 21a through 21e before prescribing these drugs in combination. When DTG, RAL, or MVC are used with rifampin for TB treatment, the ARV doses must be increased. The Phase 3 REFLATE TB2 trial compared ARV regimens including standard dose RAL 400 mg twice daily or EFV 600 mg once daily for the treatment of HIV/TB coinfection. At week 48, the standard dose RAL 400 mg twice daily regimen did not demonstrate noninferiority to EFV 600 mg once daily.²⁶ In contrast to its effect on other ARV drugs, rifampin only leads to modest reduction in EFV concentrations.^{27,28} Even though the current EFV label recommends increasing the EFV dose from 600 mg once daily to 800 mg once daily in patients weighing >50 kg,²⁹ this dosage increase is generally not necessary. A reduced dose of EFV 400 mg once daily is now approved for HIV treatment. Coadministration of EFV 400 mg with rifampin and isoniazid led to only limited changes in EFV AUC ($<25\%$) in a study with 26 participants with HIV infection, and plasma concentrations were considered adequate to maintain virologic suppression.³⁰ Until more clinical trial data are available regarding the safety and efficacy of EFV 400 mg, the Panel continues to recommend EFV 600 mg for individuals receiving

rifampin therapy.

Rifabutin, a weaker CYP3A4 enzyme inducer, is an alternative to rifampin, especially in patients receiving PI- or INSTI-based ARV regimens. Because rifabutin is a substrate of the CYP450 enzyme system, its metabolism may be affected by NNRTIs or PIs. Therefore, rifabutin dosage adjustment is generally recommended (see Tables 21a through 21e for dosing recommendations).

Rifapentine is a long-acting rifamycin which, when given daily, is a more potent inducer than rifampin.³¹ Once-daily rifapentine did not affect the oral clearance of EFV in individuals with HIV in the BRIEF TB study,³² and once weekly rifapentine has minimal impact on EFV exposure.⁷ Once-weekly rifapentine led to an increase rather than a decrease in RAL drug exposure in healthy volunteers.⁹ Once-weekly isoniazid plus rifapentine for LTBI treatment should only be given to patients receiving either an EFV 600 mg-, or RAL-based regimen (AII).

After selecting the ARV drugs and rifamycin to use, clinicians should determine the appropriate dose of each, and should closely monitor the patients to assure good control of both TB (when treating active TB) and HIV infections. Suboptimal HIV suppression or suboptimal response to TB treatment should prompt assessment of drug adherence, adequacy of drug exposure, or presence of acquired HIV or TB drug resistance.

Tuberculosis-Associated IRIS

IRIS is a clinical condition caused by ART-induced restoration of pathogen-specific immune responses to opportunistic infections such as TB, resulting in either the deterioration of a treated infection (paradoxical IRIS) or a new presentation of a previously subclinical infection (unmasking IRIS). TB-associated IRIS (TB-IRIS) has been reported in 8% to >40% of patients starting ART after TB is diagnosed, although the incidence depends on the definition of IRIS and the intensity of monitoring.^{33,34} Predictors of IRIS include a baseline CD4 count <50 cells/mm³; higher on-ART CD4 counts; high pre-ART and lower on-ART HIV viral loads; severity of TB disease, especially high pathogen burden; and <30-day interval between initiation of TB and HIV treatments.³⁵ Most IRIS in HIV/TB disease occurs ≤3 months of the start of ART.

Manifestations of unmasking TB-IRIS are characterized by their marked inflammatory nature, such as high fever, respiratory distress, lymphadenitis, abscesses, and sepsis syndrome. Manifestations of paradoxical TB-IRIS include fevers, new or worsening lymphadenopathy, new or worsening pulmonary infiltrates, enlarging pleural effusions, and new or enlarging tuberculomas.

In general, the Panel recommends continuing ART without interruption during IRIS (AIII).

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